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DYNAMICS OF RECOVERY IN DOUBLE UMBILICAL CORD BLOOD TRANSPLANTATION WITH AN EX-VIVO MESENCHYMAL CELL EXPANDED UNIT: FASTER RECOVERY WITH ENGRAFTMENT OF THE EXPANDED UNIT

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Double cord blood transplantation (CBT) with ex-vivo expansion aims at overcoming the delayed engraftment frequently observed after CBT. Thirty-one patients received myeloablative therapy with melphalan, fludarabine, thiotepa and ATG followed by double CBT for treatment of hematologic malignancies. One of the 2 units was expanded (exp) ex-vivo in a co-culture with either third party haploidentical family member marrow derived mesecnchyal stem cells (N = 8) or off-the-shelf mesenchymal progenitor cells from Angioblast (N = 23). Both CB units were matched in at least 4/6 HLA antigens with the patient, and contained a minimum of $1x10^7$ TNC/Kg per unit. The majority of patients (pts) received CBT for treatment of acute leukemia including AML / MDS (64%) and ALL (19%), and 42% were in remission at CBT. Median age was 36 years (range 2.8-62). The non-exp unit was matched with the pt in 6/6 HLA antigens in 3%, 5/6 in 26% and 4/6 in 71% of cases; the corresponding distribution for the exp unit was 6%, 29%, 64%. Engraftment was documented in 29 evaluable pts at a median of 15 (range 9 to 42) days for neutrophils and 40 (range 18 to 62) days for platelets. Day 30 chimerism showed evidence of engraftment of the non-exp unit only in 15 (52%) pts, and of both units in 13 (45%) pts, including 9 and 4 in whom the non-exp and the exp unit dominated, respectively. Chimerism was undetermined in 1 pt. Comparison of the rate of recovery in pts who had (N = 13) and those who did not have (N = 15) evidence of engraftment of the exp unit showed that neutrophils and platelet recovery was faster when the exp unit engrafted (median of 15 vs. 19 days for neutrophils; and 38 vs. 40 days for platelet). This difference did not reach statistical significance however. The median numbers of TNC and CD34+ cells infused/Kg were significantly higher in the engrafted exp than in the non-engrafted exp unit ($p < 0.05$). Sixteen pts were diagnosed with grade II-IV aGVHD including 12 within 100 days post CBT. GVHD was severe (grade III-IV) in 5 pts. On univariate analysis, there was a trend for a higher 6 month rate of grade II-IV aGVHD when the exp unit engrafted (cumulative incidence (CI) 65% vs 49%, P = 0.2); when the non-exp unit was only 4/6 HLA matched with the pt (CI 65% vs 25%), p = 0.2; and when CMV serostatus was reactive in both the recipient and in the non-exp unit (CI 77% vs 35%, p = 0.1). The investigation of CB expansion is warranted in a larger study population and accrual to our study continues.

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AN INSTITUTIONAL EXPERIENCE OF ADVERSE EFFECTS IN PATIENTS OF ADVANCED AGE USING CYCLOSPORINE AND MYCOPHENOLATE MOFETIL FOR GRAFT VERSUS HOST DISEASE PROPHYLAXIS IN REDUCED INTENSITY CONDITIONED TRANSPLANT

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Hematopoietic cell transplant in those with advanced age and/or with a higher number of co-morbid factors is a viable treatment option in this new era of reduced intensity conditioning (RIC) (McClune, et al, 2010; JCO, 2010). Based on the intensity of conditioning, RIC transplantation may require a greater degree of immune suppression to decrease the risk of graft rejection. However, greater efficacy may be counter balanced by more toxicity, particularly in older patient populations for whom these treatments are being developed. For fludarabine/TBI 200cGy conditioning with cyclosporine (CSA) and mycophenolate mofetil (MMF) graft versus host disease (GvHD) prophylaxis, CSA dosing is targeted at levels of 500-600ng/mL. In this setting, 12% of patients (median age 54) undergoing RIC procedures with these conditions experienced grade 3-5 nephrotoxicity, as defined by the NCI CTC (Diaconescu, et al, Blood, 2004). These toxicities may be even more highly accentuated in older patients. To better appreciate the prevalence and severity of adverse effects related to CSA exposure, we analyzed data from 91 patients over age 60 undergoing RIC transplant at our institution from 2001 – 2010 who received CSA/MMF GvHD prophylaxis.

Our research found numerous CSA related adverse effects including: electrolyte imbalances (100%) (hypomagnesia, hypokalemia and hyperkalemia); nephrotoxicity (88%); neurotoxicity (12%) including PRES and tremor; musculoskeletal effects in particular weakness (11%); cardiovascular impacts from CSA induced hypertension (53%) and hematologic toxicity from micro-angiopathic hemolytic anemia (1%).

The above described toxicities associated with CSA are well-known, yet in our review of this cohort of RIC transplants the incidence of CSA related adverse events was pronounced. This level of adverse events requires more aggressive monitoring and management which leads to increased resource utilization of medical personnel and dollars, and may have a negative effect on patient outcomes. In practice, we should continue to explore ways to optimize patient care while controlling expense and resource utilization, and obtain a greater understanding of the role that age and co-morbid factors have on the transplant course given the expanding role of RIC. To that end, we are currently comparing the rates of CSA-induced complications in this cohort to a group of comparable patients undergoing myeloablative transplant.

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L-LEUCYL-L-LEUCINE METHYL ESTER (LLME) TREATED NON-MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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GVHD remains an obstacle for allogeneic HSCT. While T cell depletion of donor grafts results in much lower incidences of GVHD, rejection and poor immune recovery are often associated with this approach. To address these issues, we developed a transplant approach using LLME to test the hypothesis that the selected depletion of T cells containing cytotoxic effector granules would result in less significant GVHD while at the same time preserving GVT effects and infectious immunity. LLME preferentially kills cytotoxic effector granule bearing lymphocytes including most NK and CD8 T cells with relative sparing of CD4 T cells. Fourteen patients, with a median age of 57 years with high risk disease were transplanted from related or unrelated donors after a conditioning regimen of flu/cyclo/ara-C. Prior to the infusion of the donor inoculum, we performed CD34 selection using the Isolex® system to separate the graft into CD34+ and CD34- fractions. The CD34- fraction was then treated with LLME to selectively deplete the cytotoxic effector granule containing subsets, thus avoiding stem cell exposure to LLME. Patients received the CD34 selected stem cell product (median CD34 dose 4.13 x 10^6/kg). This HSC product contained 5 x 10^4 untreated CD3 cells/kg in the initial 6 patients treated, but due to significant GVHD, the final 8 patients received 2.5 x 10^4 untreated CD3 cells/kg. One day later, the LLME treated CD34- fraction (median CD3 dose 8.74 $x10^6$ /kg) was infused. One patient died shortly after the stem cell infusion from infectious complications. All 13 evaluable patients engrafted WBC by day 14. Two patients experienced late rejection. One of these patients is still alive 3 years later with evidence of recurrent disease and the other patient eventually died of relapsed disease. Of the remaining 11 patients, 3 patients developed grade III-IV GVHD and 1 patient developed cGVHD. All 4 of these patients died of GVHD related causes. Three patients died of complications from relapsed disease and 1 additional patient died of infectious complications. Four patients are alive at a minimum of 3 years post transplant. Two of these patients have relapsed disease, 1 patient is disease free with 100% donor chimerism and one patient is disease free with a persistence of 5% host cells. This study shows that LLME can be used to treat lymphocytes without affecting initial engraftment, but relapse and GVHD remain significant barriers in this high risk population.

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MELPHALAN AND TOTAL-BODY IRRADIATION (MEL-TBI) IS AN EFFECTIVE CONDITIONING REGIMEN FOR ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT) IN PATIENTS WITH VERY POOR-RISK REFRACTORY HEMATOLOGIC MALIGNANCIES

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Introduction: Transplant outcome is poor in patients with advanced hematologic malignancies that are not in remission. We evaluated the safety and efficacy of a preparative regimen consisting of fractionated TBI (12 Gy) and MEL (100 mg/m^2 in a single dose) in 26 adult patients with refractory/relapsed AML (n = 11), ALL (n = 5), NHL (n = 5), and other malignancies (n = 5) who received allo-SCT between 2003 and 2008.

Patients and Methods: Median age was 49 (21 to 68) years and the median time from initial diagnosis to allo-SCT was 12.8 months (range, 2.3 to 58.8 months). Five patients had prior autologous SCT and 3 had prior allo-SCT. At the time of transplant, 15 (58%) had poor-risk complex cytogenetics, 10 out of 16 acute leukemia patients (63%) had circulating blasts. The stem cell product was T-cell replete in all but one patient. Thirteen patients (50%) received 8/8 matched MUD allo-SCT, 3 of whom were mismatched at one antigen or allele level. Four patients received a bone marrow product. Tacrolimus ± low dose methotrexate were used as GVHD prophylaxis in the majority of patients.

Results: One patient died on day +7 after SCT. The remaining 25 patients achieved hematopoietic engraftment with no significant delay. Treatment-related toxicity was moderate and consisted mainly of mucositis, infections and pulmonary complications such as CMV pneumonitis and diffuse alveolar hemorrhage. Three additional patients died early after SCT on days +32, +40 and +50. Median duration of hospitalization was 29 days (range, 14 to 97). Of 23 evaluable patients, 13 (57%) achieved complete remission (CR) and 7 had partial remission. Three patients had no response to transplant. Fourteen patients relapsed at a median time of 166 days (range 33-1548) after allo-SCT. Median overall survival of the entire group was 159 days. The 3-year Kaplan-Meier estimate of survival for all 26 patients was 16%. One AML patient relapsed with a different clone after remaining in CR for 4.9 years. Two patients are currently alive and in CR at 995 and 1320 days posttransplant.

Conclusions: Our early data suggest that, TBI-MEL is an active preparative regimen against acute leukemia and perhaps other advanced hematologic malignancies that are not in remission. Regimen-related toxicity is acceptable and relapse is the most common cause of treatment failure. A comparative analysis in a larger dataset is warranted to further evaluate the efficacy and safety of TB-MEL in such high-risk patients.

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SERUM FERRITIN IS A POTENTIAL PROGNOSTIC MARKER FOR TREATMENT-RELATED MORTALITY AND OVERALL SURVIVAL IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS IN TAIWAN

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In the past years, the roles of iron overloading in allogeneic hematopoietic stem trasnplnatation (allo-HSCT) had been discussed. Several articles indicated that high serum ferritin level was a poor prognostic marker, but this was not validated in Chinese population. We then established a cohort of 101 patients who received allo-HSCT in our hospital, one of the largest in Taiwan, from Jan, 2008 to Jul, 2010, and try to find if serum ferritin has any prognostic significance for them. Their median age was 32 y/o (0-61 y/o). Serum ferritin was all checked within one month before allo-HSCT (median 1692 mg/dl, ranging from 56 to 23026 mg/dl), and patients were grouped to high ferrtin group (ferritin > 1500 ng/ml, N = 56) and low ferritin group (ferritin ≤ 1500 mg/dl, N = 45) accordingly. Table 1 summerized the baseline characters of these 2 patient groups. Almost all parameters were comparable, except that there were a little more acute lymphoblastic leukemia patients in the low ferritin group. After tranplant, the engraftment kinetics in high ferritin group were comparable as those in low ferritin group (neutrophil recovery (ANC ≥ 0.5x10^9/L) 13.0±3.2 vs 13.6±6.7 days; platelet recovery (≥ 50x10^9/L) 25.6±10.8 vs 28.6±12.7 day). The incidences of acute GVHD were also comparable (22/17 vs 18/20, p = 0.45). However, trends of increased 1-year treatment-related mortality were observed in high ferritin group (26.2±7.8% vs 14.9±4.8%, p = 0.064) and then 1-year overall survival was significantly compromised in high ferritin group (62.8±8.5% vs 79.2±5.8%, p = 0.033). Relapse-free survival in high ferritin group seemed to be lower, but not yet statistically different from that in low-ferritin group (55.4±12.4% vs 83.7±4.8%, p = 0.113). From this analysis, we can conclude that in Chinese population, patients with serum ferritin ≥ 1500 mg/dl are at higher risk of treatment-related mortality and compromised overall survival when they receive allo-HSCT. However, because serum ferrtin not only is affected by body iron store but also is an indicator of systemic inflammation, whether iron cheletion therapy would benifit these patients remains unknown and well-designed prospective clinical trials are still needed for the answer.

Table 1. Comparison of the baseline characters of patients with serum level≤1500mg/dL and >1500mg/dL

	Ferritin≤1500mg/dL	Ferritin>1500mg/dL
Patient number	45	56
Age	26(0-61)	29(2-61)
Sex(M/F)	24/21	30/26
Cell Source		
BM/PB/UCB	10/34/1	8/46/2
Donor		
Sibling/Unrelated	31/15	34/22
Diagnosis		
AML/ALL/CML	12/12/2	25/7/1
MPD or MDS	5	8
Lymphoma	7	4
Others	7	11
MNC(x10^8/Kg)	9.30 ± 7.39	9.57 ± 6.55
CD34+(x10^6/Kg)	5.67 ± 3.90	5.81 ± 4.24
Conditioning regimens		
BuCy+/−ATG	17	19
TBI+Cy+/−ATG	8	8
F+Bu2y1+/−ATG	8	17
F+TBI+/−ATG	1	4
Others	11	8

ATG, anti-thymocyte globulin; F, fludarbine; TBI, total body irradiation; UCB, umbilical cord blood.

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DECITABINE AS A BRIDGING THERAPY BEFORE ALLOGENEIC STEM CELL TRANSPLANTATION FOR MYELODYSPLASTIC SYNDROME

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Decitabine is effective for myelodysplastic syndrome but is not curative. The only curative treatment is allogeneic stem cell transplantation(allo-SCT). There were few reports about pretransplant use of decitabine as a bridging therapy. We report 18 patients (median age 47, range 40-55 years, male 11, female 7) with MDS (9 patients were in IPSS Int-1, 6 patients in Int-2, and 3 patients in IPSS high) who all received at least 3 cycles of decitabine (median 4 cycles, range 3∼8 cycles) and subsequent allo-SCT(from sibling donor in 5 patients, unrelated donor in 13). Conditioning regimens consisted of FluBu4 ± ATG or low dose TBI400cGy (n = 8), FluBu2/ATG (n = 7), BuCY ± ATG (n = 2), or TBI/CY/ATG (n = 1). The source of stem cells was marrow in 1 patients and peripheral blood in 17 patients. Successful leukocyte engraftment was attained in 17/18 patients (median 12 days, range 9∼17 days). Platelet engraftment was attained in 15/18 patients (median 15 days, range 11∼31 days). Grade II∼IV skin acute GVHD were in 5/18 patients, liver or gut acute GVHD in 1/18 patients. 14/18 patients achieved a CR at 30 days after transplant. Grade II∼IV chronic GVHD were in 10 patients. With a median follow-up of 18 months (range, 6∼28 months), 11 patients are alive with CR. 7 patients have died either from relapse (n = 3) or treatment related complications (n = 4). Responders to decitabine before transplantation tend to have a better survival than non-responders. We conclude that pretransplant use of decitabine is feasible, with no increased toxicity and tend to improve the outcome of allo-SCT for MDS and should be evaluated in a prospective trial.